Is There Still a Place for Lidocaine in the (Postoperative) Management of Colics?

David E. Freeman, MVB, PhD

KEYWORDS

• Lidocaine • Colic • Horse • Postoperative reflux • Postoperative ileus
• Inflammation

KEY POINTS

- Intravenous lidocaine infusion has been widely used to prevent or treat postoperative ileus after surgery for colic in horses.
- Clinical studies support this approach, but flaws in these studies, contradictory findings from others, and the nature of the disease have raised concerns about the efficacy of lidocaine.
- Because of cost and questions about efficacy, a well-designed clinical trial is required to support continued lidocaine use.
- The analgesic properties of lidocaine as part of a multimodal strategy should be considered in select cases with postoperative colic.

INTRODUCTION

"Lidocaine has categorically been shown to have a positive effect on the small intestinal motility. It reduces ileus and acts as an anti-inflammatory, though we are not sure why. Inflammatory cells are involved with keeping the bowel from moving correctly."[1] This statement summarizes the role of lidocaine in managing horses after small intestinal surgery[1] and represents an opinion widely embraced by many equine surgeons over the last 2 decades. However, during that time, little evidence has accrued to support the role of lidocaine as a prokinetic drug or an antiinflammatory agent, although another potential role relevant to colic surgery might have emerged.

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Equine Surgery, University of Florida, College of Veterinary Medicine, Large Animal Clinical Sciences, PO Box 100136, Gainesville, FL 32610, USA
E-mail address: freemand@ufl.edu

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POSTOPERATIVE ILEUS

Postoperative ileus (POI) is defined as the failure of gastrointestinal motility to recover after colic surgery, is a common complication after small intestinal surgery in horses, and is the disease targeted by lidocaine.[2] Its importance arises through welfare concerns, prolonged hospitalization, increased costs of treatment, and reduced postoperative survival.[3] Postoperative reflux (POR) is considered more appropriate terminology than POI because it includes all causes of reflux (**Fig. 1**), including those that are purely physical (eg, anastomotic stricture).[3] For the remainder of this discussion, POI is used to designate the functional disease targeted by lidocaine as treatment or prevention, and POR is used to denote the major clinical manifestation of POI and other causes of reflux.[3]

Evidence that intravenous (IV) lidocaine can shorten the duration of POI in the human colon after abdominal surgery[4] prompted its widespread use for the same purpose after colic surgery in horses.[5–9] Its benefits in human patients with POI have been attributed to (1) reducing circulating catecholamines by inhibition of the sympathoadrenal response, (2) suppressing activity in the primary afferent neurons involved in reflex inhibition of intestinal motility, (3) stimulating smooth muscle directly, and (4) decreasing inflammation in the bowel wall through the inhibition of prostaglandin synthesis, the inhibition of granulocyte migration, and the release of lysosomal enzymes and free radicals.[4]

One of the earliest reports of using IV lidocaine in horses demonstrated that a loading dose of lidocaine followed by a continuous rate infusion (CRI) decreased halothane minimum alveolar concentration (MAC) in a dose-dependent fashion.[10] This approach to reducing the cardiovascular depressant effects of inhalants in anesthetized horses seems to be widely adopted[11] and even credited in 1 study as a possible means of preventing POI.[12] A survey of Diplomates of the American College of Veterinary Surgeons published in 2004 revealed that lidocaine CRI was the most commonly used prokinetic agent in horses after colic surgery (76% of respondents).[7] In recent surveys of European and American specialists that treat colic, IV lidocaine was used in 79% of all POI cases in Europe[8] and in 69% of such cases in the United

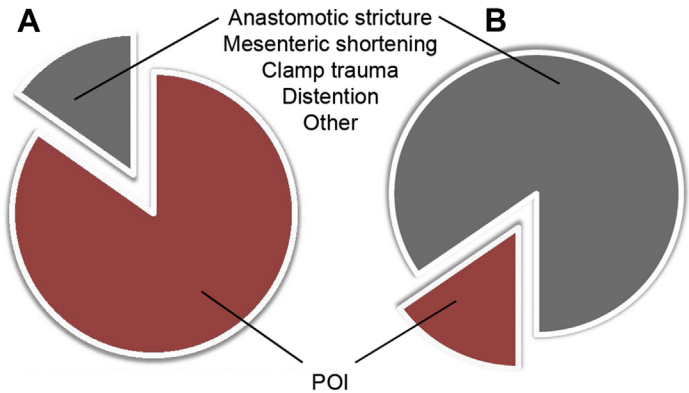

Fig. 1. Pie charts to demonstrate that POI could be one of many factors responsible for POR after small intestinal surgery, with most of the others grouped as physical causes of obstruction (anastomotic stricture, etc). The relative weighting of these factors is unknown in any individual horse with POR, but scenario A would assign POI the major role and the only opportunity for lidocaine to be effective. Repeat celiotomy could be highly effective in scenario B.

States.[9] In the same studies, 67% of European specialists used lidocaine postoperatively to prevent POI, compared with 57% in the American-based study.[8,9]

The recommended protocol for treating or preventing POI in horses with lidocaine is an initial loading dose of 1.3 mg/kg IV infused over 15 minutes, followed by 0.05 mg/kg/min in saline or lactated Ringer's solution over 24 hours.[6,13] This dose produces a serum concentration of 1 to 2 μg/mL, with 0.98 μg/mL considered the minimum therapeutic concentration.[6,13] Serum lidocaine concentrations can reach peak values during the loading infusion in awake and anesthetized horses.[14] By 3 hours after the infusion starts, horses can have a decrease in heart rate and diminished signs of existing lameness.[6] However, a significant effect on heart rate was not evident in another study, even at potentially toxic doses.[15]

METABOLISM AND PHARMACOKINETICS OF LIDOCAINE

Lidocaine IV is largely metabolized in the liver to yield increasing serum concentrations of 2 metabolites, monoethylglycinexylidide and glycinexylidide, with unknown roles in lidocaine-induced responses in horses.[5,16] Despite the substantial accumulation of these metabolites during lidocaine CRI, their concentrations and those of lidocaine return to baseline rapidly after infusion ends in healthy horses.[16] Lidocaine clearance in fed horses is approximately twice that in horses denied food, presumably because of superior hepatic blood flow in the fed state.[17]

In healthy awake horses, serum lidocaine concentrations were significantly less than in healthy anesthetized horses during loading and maintenance infusion periods in 1 study, possibly because of a decrease in cardiac output and hepatic blood flow during anesthesia.[14] These differences were not associated with adverse cardiopulmonary responses or behavioral evidence of toxicosis.[14] In a study on postoperative colic patients, lidocaine and both glycinexylidide and monoethylglycinexylidide seemed to accumulate in blood over time,[18] possibly because hepatic blood flow was reduced through hemodynamic alterations from systemic inflammation[16] and endotoxic shock.[19] This finding differs from the results of a study on lidocaine disposition in horses under anesthesia for colic surgery, in which the lidocaine concentration was lower and distribution and total body clearance values were higher than expected[20] and comparable with those recorded in healthy anesthetized horses.[14] Based on these results, horses with gastrointestinal lesions requiring surgery do not seem to require a modification of the lidocaine dose.[20]

Lidocaine is moderately protein bound in equine plasma,[21] largely to α_1-acid glycoprotein,[22] and loss of this and possibly other proteins in horses with colic could increase the plasma concentrations of lidocaine and metabolites to unsafe levels. In 1 study, the in vitro protein binding of lidocaine in equine plasma at 2 μg/mL was decreased from 53% to 29% or less when ceftiofur was given alone or combined with flunixin meglumine (FM).[21] These findings suggested that FM, which is a highly protein-bound drug, could displace lidocaine from protein and increase its unbound fraction and risk of toxicity.[21] In an in vivo study of healthy horses, the concurrent administration of lidocaine and FM did not seem to affect plasma concentration of each drug, but this study did not resolve the effects of protein binding.[23]

TOXICITY OF LIDOCAINE

Signs of toxicity in the awake horse, such as muscle fasciculations, anxiety, incoordination, ataxia, alterations in visual function, and collapse, are mediated through central nervous system effects.[15] Sudden collapse can be especially devastating in the horse after colic surgery because it can lead to some degree of dehiscence of the

ventral midline incision. Altered visual function is evident as intermittent eye blinking, anxiety, and close inspection of nearby objects.[15] Loss of consciousness, seizures, and respiratory arrest can follow severe overdosing.[24]

Lidocaine has a narrow therapeutic index so that the upper end of the effective dose closely approaches the dose at which adverse responses can develop.[24] For example, toxic effects can become evident in the 1.9 to 4.5 μg/mL range, which puts the toxic threshold in the horse at 2 to 3 times the target therapeutic level used to treat POI.[15] In a study that examined the responses of healthy horses to a slightly increased loading dose and 6 times the CRI dose, muscle fasciculations were observed at mean serum concentrations of 3.24 μg/mL.[15] In this study, clinically significant cardiovascular effects did not seem to develop in horses with serum lidocaine concentrations that induced signs of toxicity in the nervous and/or musculoskeletal systems.[15] Hypovolemia, hypoproteinemia, or both could be pronounced in horses with severe gastrointestinal disease and could lead to higher concentrations of free lidocaine in plasma than in normal horses, thereby increasing the risk of toxicity at recommended doses by body weight.

Because of rapid hepatic metabolism of lidocaine and the short half-lives of its metabolites,[16] the cessation of therapy or a reduction of the infusion rate should be instituted as soon as muscle fasciculations or other toxic responses are evident.[6,13,24] A lidocaine CRI used for balanced anesthesia should cease at least 30 minutes before the end of anesthesia to prevent the exacerbation of ataxia and incoordination in the recovery stall.[11] If seizures or excitement develop, general anesthesia might be required, but diazepam should not be used because of the risk of incoordination and delirium.[24] Other possible side effects are delayed detection of pain from laminitis[6] and an increased risk of incisional infection.[25]

MECHANISM OF ACTION OF LIDOCAINE: PROKINETIC EFFECTS

Despite the widespread use of lidocaine as a prokinetic agent,[7–9] it does not seem to have a prokinetic effect, at least in the jejunum of healthy horses after surgery to implant the electrodes used to assess motility.[26] Also, a lidocaine infusion at recommended doses can either delay[27] or have no effect on intestinal transit in healthy awake horses.[28] In an in vitro study with smooth muscle strips from healthy equine stomach and intestine, lidocaine increased the contractile activity of the proximal portion of the duodenum, but did not affect the pyloric antrum or middle portion of the jejunum.[29] However, these findings might not be relevant to the same segments in horses with inflamed intestine, in which inhibitory reflexes could dominate motility patterns.[29] Although lidocaine can improve smooth muscle contractility in vitro in equine jejunum after ischemia/reperfusion injury in vivo,[30] the concentrations required to achieve this response far exceed safe plasma concentrations. Lidocaine can block the Na^+ current through channels in jejunal circular muscle that can contribute to slow wave generation,[31] an effect that would not be expected to enhance motility. Also, coordinated pressure peaks in the equine colon can be markedly diminished by slow topical application of lidocaine around the colic arteries, and this response, if induced by systemic lidocaine, could interfere with normal colonic motility.[32]

MECHANISM OF ACTION OF LIDOCAINE: ANTIINFLAMMATORY EFFECTS

The putative antiinflammatory effects of lidocaine could be of benefit to horses with POI because of the proposed role of inflammation in the pathogenesis of this complication.[33] The current hypothesis for development of POI proposes an early neurogenic

and a later inflammatory response to gastrointestinal surgery,[33] which has recently been incorporated into 4 phases, as follows[34]:

- An early neurogenic phase caused by surgery and mediated through the activation of mesenteric and splanchnic afferent nerves, eventually leading to impaired motility through nitrergic and adrenergic effects.[34] This phase usually ends with termination of surgery.[34]
- An early phase of inhibited smooth muscle function (lasting until 6 hours after intestinal manipulation) mediated in part by innate cytokines released, most likely by resident macrophages. This inflammatory phase is probably triggered by intestinal manipulation and involves interaction between the immune system, the autonomic nervous system, and gastrointestinal smooth muscle.[34]
- A second phase of smooth muscle inhibition starts after approximately 6 hours, is temporally associated with the influx of inflammatory cells, and lasts until 24 hours after intestinal manipulation.
- The final phase involves alterations in enteric neurotransmission and cholinergic activity that can persist after the recovery of gastrointestinal transit.[34]

Lidocaine can inhibit neutrophil adhesion, migration, phagocytosis, and free radical production,[35] can downregulate nuclear factor-$\kappa\beta$ signaling,[36] and inhibit tumor necrosis factor-α, IL-2, and IL-8 production during inflammation induced by ischemia.[36–38] Despite these potential beneficial effects in other animals, there is little evidence that lidocaine might actually produce an antiinflammatory effect in any organ in horses. In an in vitro study on equine neutrophils, lidocaine did not inhibit neutrophil migration or adhesion at therapeutic concentrations, and it actually increased migration and adhesion at potentially toxic concentrations.[39] It also failed to reduce the expression of proinflammatory genes in lipopolysaccharide-stimulated equine monocytes.[40] Despite its ability to decrease inflammation and improve lung function in human asthmatic patients, lidocaine seemed to increase total cell numbers and the percentage of neutrophils in the bronchoalveolar lavage fluid from horses with recurrent airway obstruction.[41] In the black walnut model of laminitis, lidocaine increased laminar E-selectin messenger RNA concentrations and did not inhibit inflammatory events in either the laminae or the skin.[42] Systemic lidocaine at levels used to manage laminitic pain failed to change surface expression of CD13 and CD18 markers of neutrophil activation in horses that received black walnut extract.[43] In a study in which horses received intraperitoneal endotoxin, the clinical score and tumor necrosis factor-α activity were significantly lower in those treated with lidocaine than in a saline-treated group.[44] However, lidocaine had no effect on the polymorphonuclear neutrophils (PMN) cell count, fibrinogen, and total protein in peritoneal fluid and did not change IL-6 production.[44]

Lidocaine combined with FM ameliorated the inflammation (based on mucosal neutrophil counts) associated with FM alone at 18 hours of reperfusion after ischemia in adult horses.[45] In the same study, lidocaine administered IV during reperfusion reduced plasma prostaglandin E_2 metabolite concentration and mucosal cyclooxygenase-2 expression in ischemia-injured jejunum.[45] In more recent studies on transmural inflammation induced by ischemia/reperfusion or manipulation in equine jejunum and ischemia/reperfusion in equine colon, lidocaine did not blunt the inflammatory response in any intestinal layer.[46] Lidocaine did decrease cyclooxygenase-2 expression in circular muscle and through all layers combined in manipulated jejunum, but the response was not consistent and was absent in postischemic segments.[46] In another ischemia/reperfusion model in horse jejunum, moderate to severe pulmonary inflammation developed as a remote organ response, with the

recruitment of neutrophils and inflammatory molecules.[47] Lidocaine decreased the pulmonary neutrophil response, but without affecting other markers of inflammation and was associated with an increase in pulmonary macrophages.[47] These findings led to an inconclusive assessment of the antiinflammatory benefits of lidocaine in this model.[47] In a study of remote organ responses in equine liver, lung, and kidney to intestinal injury induced by ischemia/reperfusion and jejunal manipulation, lidocaine did not blunt inflammation in these organs.[48]

MECHANISM OF ACTION OF LIDOCAINE: VISCERAL ANALGESIA

Perioperative lidocaine provides considerable pain relief for human patients undergoing abdominal surgery, sufficient to decrease postoperative opioid requirements and thereby reduce the adverse effects of these drugs on intestinal function.[49] This visceral pain relief could be partly explained by the inhibition of spinal neuronal populations excited by intestinal distension.[50] Anecdotal evidence has emerged that lidocaine also provides visceral analgesia in horses, although the available scientific information is inconclusive. One study had technical limitations that prevented the recording of lidocaine effects on visceral pain in a statistically meaningful number of horses.[51] However, in a study on recovery from ischemia/reperfusion in equine jejunum, lidocaine combined with FM had superior pain scores than lidocaine or FM alone.[52] This apparent benefit of lidocaine as a component of a multimodal approach to analgesia could be useful in managing horses with postoperative colic after small intestinal surgery or large colon resection. Pain relief could be of benefit in managing POI, because pain could play a contributory role in the early and late phases of this complication by mediating a sympathetic efferent response that decreases intestinal motility.[53]

MECHANISM OF ACTION OF LIDOCAINE: MISCELLANEOUS

The perceived clinical benefits of lidocaine in horses after colic surgery could also be attributed to miscellaneous effects mediated through specific peripheral and central Na^+ channels.[24] Lidocaine can prevent fluid secretion into the small intestinal lumen and decrease edema formation in the intestinal wall in rats,[54–56] effects that could benefit horses with POR or duodenitis proximal jejunitis. Lidocaine could ameliorate the increased lipopolysaccharide permeability associated with the apparent adverse effects of FM on recovery of the mucosal barrier in equine jejunal mucosa.[52] By decreasing mucosal injury and improving intestinal repair in equine jejunum and the right dorsal colon after ischemia, lidocaine could decrease the output of neutrophil chemoattractants from damaged tissue at these sites.[40]

EFFICACY OF LIDOCAINE IN THE PREVENTION AND TREATMENT OF POSTOPERATIVE ILEUS

Although POI is the postoperative complication at which lidocaine is directed for treatment and prevention, this is a difficult complication to study, for the following reasons.

- Reflux through a nasogastric tube or POR is the hallmark of POI, but could also be caused by a physical obstruction, without any indicators that would distinguish between the 2 causes.[2,3] Therefore, POI might be part of a multifactorial disease, and with an unknown overall contribution to severity of that disease (see **Fig. 1**).[3] Without surgery or necropsy, POI is only a presumptive diagnosis in any horse with POR.[3]
- In horses subjected to repeat celiotomy in a recent study, 81% responded with a complete cessation of POR after the second surgery, despite a second bout of

surgical manipulation and associated inflammation.[57] These findings demonstrate 2 ways in which lidocaine could fail in management of POR: first, the target abnormality for lidocaine (inflammation) is not the predominant cause of POR, and second, the predominant cause of POR in this study[57] and probably others (physical obstruction) is not affected by lidocaine (see **Fig. 1**).

- In 1 prospective study,[13] 19 horses with POR were excluded because reflux ceased at the onset of lidocaine/saline infusion, raising the possibility that resolution of POR during these infusions could also be a spontaneous event.[58] This is a complicating issue in studying the treatment of any disease capable of spontaneous resolution.[58]
- Cessation of POR with medical treatment could also be caused by spontaneous resolution of a physical obstruction or adaptation to it over time (eg, adhesion, anastomotic stricture), and not to a favorable response of POI to treatment.

The results of 4 studies that examined the effects of a lidocaine CRI in horses after colic surgery supported its role for treatment or prevention of POI[12,13,59,60] (**Table 1**). However, these studies have flaws in their design or interpretation that diminish their impact, largely through insufficient study power (see **Table 1**). Also grouping large and small intestinal obstructions together and including duodenitis proximal jejunitis, presumably to increase the power of data analysis, could introduce different elements of pathogenesis and hence different responses to treatment. One retrospective study found that lidocaine CRI had no effect on the prevalence of POR, total reflux volume, duration of reflux, or survival after surgery for small intestinal colics in horses.[61] In this study, the cohorts for comparison were grouped by period of hospital admission, an early period when lidocaine was not used and later when it was. Therefore, assignment to treatment group was not random and also horses at risk of POR or that developed POR were more likely to be treated with lidocaine in this study.[61] Despite limitations related to the retrospective, nonrandomized nature of this study, the 2 groups were similar for most variables measured.[61] As with any retrospective, nonblinded studies, the latter study and possibly others (see **Table 1**) that have investigated lidocaine[12,60] have important potential biases that could render them unsuitable for meta-analysis.[62]

Important information about the benefit of any drug can be gained through studies that examine prevalence of the target disease when the drug in question is not used. Four interrelated studies demonstrated that low rates of POR were achieved after small intestinal surgery in horses without lidocaine, despite use of very inclusive criteria for POR.[63–66] These studies also used an approach to small intestinal surgery that gave every horse with a financial option for surgery a chance, regardless of disease severity, type of anastomosis indicated, and need for repeat celiotomy.[64–66] In one of these studies, no horse had POR after jejunojejunostomy.[65] By contrast, POR rates of 63% were recorded in a similar study, but with postoperative lidocaine infusion.[67] These findings underscore the importance of other factors on outcome in clinical trials on colic surgery.[68]

CONCERNS ABOUT USE OF LIDOCAINE

In the absence of an established effect of lidocaine as a prokinetic drug through direct or indirect mechanisms, the negative implications of its use need to be considered. The risk and nature of toxic effects would be acceptable, especially if the benefits were more favorable. The cost of treatment with lidocaine can be high because of the volumes required for the bolus infusion and a 24-hour (or longer) CRI, and for use of a fluid pump to ensure a safe rate of delivery. The cost of colic surgery probably

Table 1
Four studies that yielded favorable responses to lidocaine as treatment or as a prophylactic measure against POI

	Brianceau et al,[59] 2002, *JVIM*	Cohen et al,[12] 2004, *JAVMA*	Malone et al,[13] 2006, *Vet Surg*	Torfs et al,[60] 2009, *JVIM*
Study type	Randomized controlled trial, blinded, 13 lidocaine-treated horses and 15 saline controls with surgery for intestinal disease	Prospective case-control study on risk factors for POI in 2 hospital populations	Randomized controlled trial, double-blinded, prospective study, multicenter, with 17 treated horses and 15 controls	Retrospective cross-sectional study 126 horses (67% strangulating, 33% nonstrangulating lesions) 44% of all horses had SI resection and anastomosis
Timing	Intraoperative administration and continued for 24 hours postoperatively; loading dose followed by CRI	Intraoperative administration of lidocaine (details of doses not given)	24-hour CRI after lidocaine bolus Horses included if a presumptive diagnosis of duodenitis proximal jejunitis or POI with gastric reflux; no motility agents permitted in the 24 hours before and 36 hours after treatment	Horses were started on lidocaine CRI after administration of loading bolus during anesthesia (all but 11 horses). Prophylactic lidocaine after anesthesia (bolus and CRI) Horses received nonrandomized treatment with prokinetic drugs (88%); some were administered prophylactically and others once POR had developed Many horses received concurrent multiple prokinetic drugs
Results	Lidocaine CRI significantly reduced jejunal cross-section and peritoneal fluid accumulation on ultrasound examination. No effect on gastrointestinal sounds, time to passage of feces, number of defecations in first 24 hours, gastric reflux, duodenal or jejunal wall thickness, maximum duodenal or jejunal diameter or cross-sectional area, small-intestinal contractions per minute, rate of complications, or outcome.	POI developed in 47 of 251 horses Marginal association with reduced likelihood of POI with lidocaine; the inclusion of the variable intraoperative lidocaine improved model fit and hence this variable was retained	65% of treated horses with POI stopped refluxing within 30 hours, compared with 27% in the placebo group ($P = .04$) Reduced hourly volume of reflux and decreased duration of hospitalization in the lidocaine compared with the placebo group No effect on survival between lidocaine and placebo groups	Decreased risk of POI with lidocaine (51% compared with 21%) Survival odds: 3.33 times higher with lidocaine 34% survival from POI

Flaws	Low study power and few had small intestinal lesions (n = 4 in lidocaine, n = 4 in saline group) Low prevalence of gastric reflux (n = 1 in lidocaine and n = 1 in saline group) so unable to investigate effect of lidocaine on POI	Lidocaine administration biased toward 1 hospital population Not randomized and unknown if preferential administration to horses more likely to develop POI	Lidocaine or placebo was only started after the onset of postoperative reflux and therefore cannot be used to assess its use to prevent POR No selection criteria described Duodenitis proximal jejunitis horses grouped with POI Included types of colic not typically associated with POI (colon diseases, impactions, duodenitis proximal jejunitis) Little overlap in study periods between hospitals Small numbers in different categories – low power	No apparent randomization of treatment Potential biases, for example, assignment to lidocaine group All but 11 horses received lidocaine under anesthesia Only 35 horses in the nonlidocaine group and unclear if these horses received other prokinetic drugs No apparent blinding 79% of control horses received lidocaine under anesthesia Lidocaine combined with prokinetic drugs – low power in treatment categories and role of other drugs unknown Small numbers in different categories – low power

leads to more deaths among the general equine population with this devastating disease than disease-related factors, so that the cost to benefit ratio for lidocaine might not be acceptable. The low rate of POR recorded in studies that did not use lidocaine[63–66] suggests that POR might be a complicated disease in horses, with mixed elements of physical and functional causes that we need to unravel.

SUMMARY

The effectiveness of lidocaine as a prokinetic drug (whether through direct or indirect mechanisms) is controversial. The favorable results in horses with small intestinal disease not treated with lidocaine challenge any notions about the need to use it. However, selective use, as opposed to the current almost routine use, should be considered for horses in which a multimodal form of analgesia is required, especially combined with FM.[52] In such cases, lidocaine would offer the benefit over other analgesic drugs of having little if any adverse effect on intestinal motility. Suitable candidates would include horses that are painful after large colon resection or any gastrointestinal surgery, but with a level of pain that is manageable on the humane level. Care must be taken in postoperative small intestinal cases to ensure that signs of pain indicative of the need for repeat celiotomy are not masked by overzealous use of any analgesic drugs. The current routine use of lidocaine as a prophylactic measure against POR after small intestinal surgery is not justified, unless a large, well-designed multicenter, blinded, randomized, controlled trial proves otherwise. That POR would respond to treatment with one drug seems unrealistic, based on consideration of possible causes of this disease.

REFERENCES

1. Blikslager AT, Tiffany LM. Lots of theories, few answers on colic. Veterinary Practice News 2011;41–2. Available at: https://www.veterinarypracticenews.com/lots-of-theories-few-answers-on-colic/.
2. Merritt AM, Blikslager AT. Post operative ileus: to be or not to be? Equine Vet J 2008;40(4):295–6.
3. Freeman DE. Post-operative reflux – a surgeon's perspective. Equine Vet Educ 2018;30:671–80.
4. Rimback G, Cassuto J, Tollesson PO. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. Anesth Analg 1990;70:414–9.
5. Cook VL, Blikslager AT. Use of systemically administered lidocaine in horses with gastrointestinal tract disease. J Am Vet Med Assoc 2008;232:1144–8.
6. Malone ED, Turner TA, Wilson JH. Intravenous lidocaine for the treatment of ileus in the horse. In Proceedings of 5th Equine Colic Research Symposium, University of Georgia, Athens, 1994, p. 39.
7. Van Hoogmoed LM, Nieto JE, Snyder JR, et al. Survey of prokinetic use in horses with gastrointestinal injury. Vet Surg 2004;33:279–85.
8. Lefebvre D, Pirie RS, Handel IG, et al. Clinical features and management of equine post operative ileus: survey of diplomates of the European Colleges of Equine Internal Medicine (ECEIM) and Veterinary Surgeons (ECVS). Equine Vet J 2016;48:182–7.
9. Lefebvre D, Hudson NPH, Elce YA, et al. Clinical features and management of equine post operative ileus (POI): survey of diplomates of the American Colleges of Veterinary Internal Medicine (ACVIM), Veterinary Surgeons (ACVS) and Veterinary Emergency and Critical Care (ACVECC). Equine Vet J 2016;48:714–9.

10. Doherty TJ, Frazier DL. Effect of intravenous lidocaine on halothane minimum alveolar concentration in ponies. Equine Vet J 1998;30(4):300–3.
11. Valverde A. Balanced anesthesia and constant-rate infusions in horses. Vet Clin North Am Equine Pract 2013;29:89–122.
12. Cohen ND, Lester GD, Sanchez LC, et al. Evaluation of risk factors associated with development of postoperative ileus in horses. J Am Vet Med Assoc 2004; 225:1070–8.
13. Malone E, Ensink J, Turner T, et al. Intravenous continuous infusion of lidocaine for treatment of equine ileus. Vet Surg 2006;35:60–6.
14. Feary DJ, Mama KR, Wagner AE, et al. Influence of general anesthesia on pharmacokinetics of intravenous lidocaine infusion in horses. Am J Vet Res 2005;66: 574–80.
15. Meyer GA, Lin HC, Hanson RR, et al. Effects of intravenous lidocaine overdose on cardiac electrical activity and blood pressure in the horse. Equine Vet J 2001;33: 434–7.
16. Dickey EJ, McKenzie HC III, Brown JA, et al. Serum concentrations of lidocaine and its metabolites after prolonged infusion in healthy horses. Equine Vet J 2008; 40:348–52.
17. Engelking LR, Blyden GT, Lofsledt J, et al. Pharmacokinetics of antipyrine, acetaminophen and lidocaine in fed and fasted horses. J Vet Pharmacol Ther 1987; 10:73–82.
18. de Solís CN, McKenzie HC III. Serum concentrations of lidocaine and its metabolites MEGX and GX during and after prolonged intravenous infusion of lidocaine in horses after colic surgery. J Equine Vet Sci 2007;27:398–404.
19. McKindley DS, Boulet J, Sachdeva K, et al. Endotoxic shock alters the pharmacokinetics of lidocaine and monoethylglycinexylidide. Shock 2002;17:199–204.
20. Feary DJ, Mama KR, Thomasy SM, et al. Influence of gastrointestinal tract disease on pharmacokinetics of lidocaine after intravenous infusion in anesthetized horses. Am J Vet Res 2006;67:317–22.
21. Milligan M, Kukanich B, Beard W, et al. The disposition of lidocaine during a 12-hour intravenous infusion to postoperative horses. J Vet Pharmacol Ther 2006;29: 495–9.
22. Routledge PA, Barchowsky A, Bjornsson TD, et al. Lidocaine plasma protein binding. Clin Pharmacol Ther 1980;27:347–51.
23. Waxman SJ, Kukanich B, Milligan M, et al. Pharmacokinetics of concurrently administered intravenous lidocaine and flunixin in healthy horses. J Vet Pharmacol Ther 2011;35:413–6.
24. Vigani A, Garcia-Pereira FL. Anesthesia and analgesia for standing equine surgery. Vet Clin Equine 2014;30:1–17.
25. Stephen JO, Corley KT, Johnston JK, et al. Factors associated with mortality and morbidity in small intestinal volvulus in horses. Vet Surg 2004;33:40–348.
26. Milligan M, Beard W, Kukanich B, et al. The effect of lidocaine on postoperative jejunal motility in normal horses. Vet Surg 2007;36:214–20.
27. Rusiecki KE, Nieto JE, Puchalski SM, et al. Evaluation of continuous infusion of lidocaine on gastrointestinal tract function in normal horses. Vet Surg 2008;37: 564–70.
28. Elfenbein JR, Robertson SA, MacKay RJ, et al. Systemic and anti -nociceptive effects of prolonged lidocaine, ketamine, and butorphanol infusions alone and in combination in healthy horses. BMC Vet Res 2014;10(Suppl 1):S6.
29. Nieto JE, Rakestraw PC, Snyder JR, et al. In vitro effects of erythromycin, lidocaine, and metoclopramide on smooth muscle from the pyloric antrum, proximal

portion of the duodenum, and middle portion of the jejunum of horses. Am J Vet Res 2000;61:413–9.
30. Guschlbauer M, Hoppe S, Geburek F, et al. In vitro effects of lidocaine on the contractility of equine jejunal smooth muscle challenged by ischaemia-reperfusion injury. Equine Vet J 2010;42:53–8.
31. Holm AN, Rich A, Miller SM, et al. Sodium current in human jejunal circular smooth muscle cells. Gastroenterology 2002;122:178–87.
32. Sellers AF, Lowe JE, Brondhum J. Motor events in equine large colon. Am J Physiol 1979;237:E457–64.
33. Bauer AJ, Schwarz NT, Moore BA, et al. Ileus in critical illness: mechanisms and management. Curr Opin Crit Care 2002;8:152–7.
34. Farro G, Gomez-Pinilla PJ, Di Giovangiulio M, et al. Smooth muscle and neural dysfunction contribute to different phases of murine postoperative ileus. Neurogastroenterol Motil 2016;28:934–47.
35. Azuma Y, Shinohara M, Wang PL, et al. Comparison of inhibitory effects of local anesthetics on immune functions of neutrophils. Int J Immunopharmacol 2000;22:789–96.
36. Lahat A, Horin SB, Lang A, et al. Lidocaine down-regulates nuclear factor-κβ signalling, and inhibits cytokine production and T cell proliferation. Clin Exp Immunol 2008;152:320–7.
37. Lan W, Harmon D, Wang JH, et al. The effect of lidocaine on neutrophil CD11b/CD18 and endothelial ICAM-1 expression and IL-1β concentrations induced by hypoxia-reoxygenation. Eur J Anaesthesiol 2004;21:967–72.
38. Lang A, Horin SB, Picard O, et al. Lidocaine inhibits epithelial chemokine secretion via inhibition of nuclear factor κβ activation. Immunobiology 2010;215:304–13.
39. Cook VL, Neuder LE, Blikslager AT, et al. The effect of lidocaine on in vitro adhesion and migration of equine neutrophils. Vet Immunol Immunopathol 2009;129:137–42.
40. Cook VL. Lidocaine: we all use it – now we know why. In: Proceedings of the International Veterinary Emergency and Critical Care Symposium 2012, San Antonio, Texas. Available at: https://www.vin.com/Members/login/login.aspx?ReturnUrl=/members/proceedings/Proceedings.plx?CID=IVECCS2012&Category=&PID=85257&O=VIN. Accessed April 9, 2019.
41. Wilson ME, Berney C, Behan A, et al. Lidocaine does not prevent neutrophil influx or attenuate lung function in heaves-affected horses. J Vet Intern Med 2012;26:1427–32.
42. Williams JM, Lin YJ, Loftus JP, et al. Effect of intravenous lidocaine administration on laminar inflammation in the black walnut extract model of laminitis. Equine Vet J 2010;42:261–9.
43. Loftus JP, Williams JM, Belknap JK, et al. In vivo priming and ex vivo activation of equine neutrophils in black walnut extract-induced equine laminitis is not attenuated by systemic lidocaine administration. Vet Immunol Immunopathol 2010;138:60–9.
44. Peiro JR, Barnabe PA, Cadioli FA, et al. Effects of lidocaine infusion during experimental endotoxemia in horses. J Vet Intern Med 2010;24:940–8.
45. Cook VL, Jones Shults J, McDowell MR, et al. Anti-inflammatory effects of intravenously administered lidocaine hydrochloride on ischemia-injured jejunum in horses. Am J Vet Res 2009;70:1259–68.

46. Bauck AG, Grosche A, Morton AJ, et al. Effect of lidocaine on inflammation in equine jejunum subjected to manipulation only and remote to intestinal segments subjected to ischemia. Am J Vet Res 2017;78:977–89.
47. Montgomery JB, Hamblin B, Suri SS, et al. Remote lung injury after experimental intestinal ischemia-reperfusion in horses. Histol Histopathol 2014;29:361–75.
48. Daggett J, Grosche A, Abbott J, et al. Remote responses to intestinal ischemia and reperfusion injury in equine colon and jejunum. In: Proceedings of 12th International Equine Colic Research Symposium Lexington (KY): 2017, p. 39.
49. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery. A systematic review of randomized controlled trials. Drugs 2010;70:1149–63.
50. Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. Anesthesiology 2000;92:1685–91.
51. Robertson SA, Sanchez LC, Merritt AM, et al. Effect of systemic lidocaine on visceral and somatic nociception in conscious horses. Equine Vet J 2005;37:122–7.
52. Cook VL, Jones Shults J, McDowell M, et al. Attenuation of ischaemic injury in the equine jejunum by administration of systemic lidocaine. Equine Vet J 2008;40:353–7.
53. Fukuda H, Tsuchida D, Koda K, et al. Inhibition of sympathetic pathways restores postoperative ileus in the upper and lower gastrointestinal tract. J Gastroenterol Hepatol 2007;22:1293–9.
54. Nellgard P, Jonsson A, Bojo L, et al. Small-bowel obstruction and the effects of lidocaine, atropine and hexamethonium on inflammation and fluid losses. Acta Anaesthesiol Scand 1996;40:287–92.
55. Cassuto J, Jodal M, Tuttle R, et al. The effect of lidocaine on the secretion induced by cholera toxin in the cat small intestine. Experientia 1979;35:1467–8.
56. Larsson MH, Sapnara M, Thomas EA, et al. Pharmacological analysis of components of the change in transmural potential difference evoked by distension of rat proximal small intestine in vivo. Am J Physiol Gastrointest Liver Physiol 2008;294(1):G165–73.
57. Bauck AG, Easley JT, Cleary OB, et al. Response to early repeat celiotomy in horses after a first surgery for jejunal strangulation. Vet Surg 2016;46:843–50.
58. Nolen-Walston R, Paxson J, Ramey DW. Evidence-based gastrointestinal medicine in horses: it's not about your gut instincts. Vet Clin North Am Equine Pract 2007;23:243–66.
59. Brianceau P, Chevalier H, Karas A, et al. Intravenous lidocaine and small-intestinal size, abdominal fluid, and outcome after colic surgery in horses. J Vet Intern Med 2002;16:736–41.
60. Torfs S, Delesalle C, Dewulf J, et al. Risk factors for equine postoperative ileus and effectiveness of prophylactic lidocaine. J Vet Intern Med 2009;23:606–11.
61. Salem SE, Proudman CJ, Archer DC. Has intravenous lidocaine improved the outcome in horses following surgical management of small intestinal lesions in a UK hospital population? BMC Vet Res 2016;12:157.
62. McKenzie JE, Beller EM, Forbes AB. Introduction to systematic reviews and meta-analysis. Respirology 2016;21:626–37.
63. Freeman DE, Hammock P, Baker GJ, et al. Short and long-term survival and prevalence of postoperative ileus after small intestinal surgery in the horse. Equine Vet J 2000;(Suppl 32):42–51.
64. Freeman DE, Schaeffer DJ. A comparison of handsewn versus stapled jejunocecostomy in horses - complications and long-term survival: 32 cases (1994-2005).

J Am Vet Med Assoc 2010;237:1060–7 [Erratum appears in J Am Vet Med Assoc 2011;238:65].
65. Freeman DE, Schaeffer DJ. Clinical comparison between a continuous Lembert pattern wrapped in a carboxymethylcellulose and hyaluronate membrane with an interrupted Lembert pattern for one-layer jejunojejunostomy in horses. Equine Vet J 2011;43:708–13.
66. Freeman DE, Schaeffer DJ, Cleary OB. Long-term survival in horses with strangulating obstruction of the small intestine managed without resection. Equine Vet J 2014;46:711–7.
67. Close K, Epstein KL, Sherlock CE. A retrospective study comparing the outcome of horses undergoing small intestinal resection and anastomosis with a single layer (Lembert) or double layer (simple continuous and Cushing) technique. Vet Surg 2014;43:471–8.
68. Smith MA, Edwards GB, Dallap BL, et al. Evaluation of the clinical efficacy of prokinetic drugs in the management of post-operative ileus: can retrospective data help us? Vet J 2005;170:230–6.